Original Study

Outcomes of Treatment in Slovene Follicular Lymphoma Patients

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Abstract

The treatment outcomes of follicular lymphoma (FL) patients have been positively influenced by the introduction of rituximab in the last 2 decades. A retrospective analysis of progression-free survival and overall survival of 278 routinely treated Slovene FL patients confirmed the significant benefit of adding rituximab to chemotherapy and into the maintenance setting outside clinical studies.

Background: The outcome of follicular lymphoma (FL) patients has dramatically improved over the last 2 decades by introduction of rituximab in combination chemotherapy and into maintenance setting. We retrospectively analyzed the treatment outcomes in Slovene FL patients in the era of rituximab and compared them to the results reported by pivotal clinical studies. **Patients and Methods:** Two hundred seventy-eight patients with FL treated in Slovenia between 2000 and 2010 with a median follow-up of 5.7 years were included in our retrospective analysis. One hundred ninety-three (69%) received systemic treatment (ST). **Results:** With a median follow-up of 5.7 years, the 5- and 10-year overall survival (OS) rates for the whole series were 77% and 53%, respectively. The 5-year progression-free survival (PFS) for 193 FL patients treated with ST was 37%. Patients treated with rituximab chemotherapy had a significantly better OS than patients treated with chemotherapy alone, with a 5-year OS of 79% versus 53% (hazard ratio [HR], 0.39; 95% confidence interval [CI], 0.22-0.67; $P = .001$). Adding rituximab to the first-line chemotherapy significantly improved PFS compared to chemotherapy alone (HR, 0.26; 95% CI 0.18-0.36; $P < .001$). Maintenance rituximab after immunochemotherapy in first-line treatment reduced the risk for progression by 61% and significantly prolonged the time to progression (HR, 0.39; 95% CI 0.20-0.73; $P < .003$). **Conclusion:** The outcomes in our routinely treated FL patients confirm the benefit of adding rituximab to chemotherapy and are comparable to the results of pivotal clinical studies. The outcome of our FL patients was improved in terms of both PFS and OS.

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Introduction

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin lymphoma, comprising 20% to 30% of all lymphomas and approximately 70% of indolent lymphomas. The median age at diagnosis is 60 years. Clinically, the disease is characterized by an indolent course, with waxing and waning lymphadenopathy, slowly progressing over the years. Most patients are diagnosed with advanced-stage disease; despite the major progress that has been made in the management of the disease, it is still considered incurable.[1,2]

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The optimal management strategy of FL has not yet been defined. Current treatment approaches vary from watchful waiting to combination chemotherapy and allogeneic transplantation.[3] The watch-and-wait strategy remains a safe option for patients without disease-related symptoms because randomized studies have not demonstrated a survival benefit with early application of systemic therapy.[4] With the introduction of the anti-CD20 monoclonal antibody rituximab, the prognosis of FL patients has dramatically changed over the past 2 decades. The benefit of adding rituximab to combination chemotherapy has been proved in multiple randomized trials, all of which demonstrated improvement in response rates, time to progression, and improvement in survival.[5-9] Additional benefit in the outcome of FL patients has been proven by introduction of rituximab in the maintenance setting. Several prospective randomized studies have shown the beneficial effect of rituximab maintenance therapy in patients with previously untreated and relapsed FL.[10-14] The results of the PRIMA study established rituximab maintenance

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therapy as a new standard of care for the first-line treatment of patients who experience remission after immunochemotherapy.[15]

With the modern rituximab chemotherapeutic regimens, the median survival of FL patients has been prolonged from 8 to 10 years to 12 to 15 years.[3,16-18] Hence, the introduction of rituximab into therapy represents an important step forward in the management of this disease and has become the standard of care in first-line, relapse, and maintenance treatment of FL patients.[19]

According to cancer registry data, Slovenia has about 65 new cases of FL per year, with an incidence rate of 2.8 per 100,000 persons for both men and women, which represents approximately 20% of all non-Hodgkin lymphoma cases in Slovenia.[20]

The aim of our retrospective study of 278 FL patients was to analyze the treatment outcome in Slovene FL patients, to evaluate the benefit of adding rituximab to combination therapy, and to compare the results to the outcomes of FL patients reported by major clinical studies.

Patients and Methods

Patients

Two hundred seventy-eight patients diagnosed with FL treated at the Institute of Oncology and other Slovene hospitals between 2000 and 2010 were included in our retrospective analysis.

Methods

Treatment decisions were based primarily on consensus recommendations at the time. After the completion of primary treatment, patients underwent regular follow-up examinations at our institute. Patient and disease characteristics, treatment, and survival outcomes were evaluated retrospectively from patients' records. All procedures were compliant with the ethical standards of the local institutional ethical committee.

Statistical Analysis

The outcome variables analyzed were progression-free survival (PFS) and overall survival (OS), defined according to the criteria of Cheson et al.[21] The PFS was calculated from the date of starting treatment to the first occurrence of relapse, disease progression or death, or last follow-up. OS was defined as the time interval between the date of diagnosis of lymphoma and last follow-up or death. Survival curves were plotted by the Kaplan-Meier method, and the log rank test was applied to analyze statistical differences in survival.[22] Cox multivariate hazard models were used to calculate the hazard ratios (HR) and their 95% confidence intervals (CI) in the analysis of PFS and OS. All reported *P* values are 2-tailed. SPSS version 19.0 was used for all statistical analysis (IBM, Armonk, NY).

Results

Patient Characteristics and Treatment

Baseline characteristics are presented in Table 1. A total of 278 patients with FL were included in our analysis. The median age was 58 years; 128 patients (46.1%) were older than 60 years. There were 59.4% women and 40.6% men included. Thirty-four percent of the patients had limited-stage disease, and almost 65% had advanced-stage disease at the time of diagnosis. According to histopathologic grade, 50% had low-grade FL (grade 1 or 2), 27.3% were grade 3, and 5% were combined FL and diffuse large B-cell lymphoma. In 48 patients, the grade was not defined. According to Follicular Lymphoma International Prognostic Index (FLIPI) score, 45% were considered low risk, 26% intermediate risk, and 26.6% high risk.

Table 1 Patient Characteristics

Characteristic	All Patients (n = 278)	Patients With ST (n = 193)
Age (Years)		
≥60, n (%)	128 (46.1)	87 (45.0)
Median (range)	58 (20-90)	57 (20-90)
Gender, n (%)		
Male	113 (40.6)	78 (40.0)
Female	165 (59.4)	115 (60.0)
Stage, n (%)		
I	53 (19.1)	15 (7.7)
II	43 (15.5)	27 (14.0)
III	53 (19.1)	36 (18.6)
IV	127 (45.7)	114 (59.0)
Not determined	2	1
Grade, n (%)		
1	35 (12.6)	24 (12.4)
2	105 (37.8)	68 (35.2)
3	76 (27.3)	53 (27.4)
FL + DVCBL	14 (5.0)	14 (7.2)
Not determined	48 (17.3)	34
FLIPI Score, n (%)		
Low (0-1)	125 (44.9)	62 (32.0)
Intermediate (2)	72 (25.9)	59 (30.5)
High (3-5)	74 (26.6)	67 (34.7)
Not determined	7	5

Abbreviations: FL + DLBCL = follicular lymphoma + diffuse large B cell lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; ST = systemic treatment.

One hundred ninety-three of all patients who needed therapy received systemic treatment (ST). The induction regimen was R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) in 54.4%, 4 patients received R-CVP (rituximab, cyclophosphamide, doxorubicin, vincristine), and 2 patients received rituximab combined with other chemotherapy regimens. The other 82 patients (42.5%) received chemotherapy alone as an induction regimen, with CHOP (n = 26) and CVP (n = 39) being the regimens most often provided. Seventeen patients received chlorambucil. Among 111 patients who received rituximab chemotherapy as first-line treatment, 66 continued with maintenance rituximab. There were no statistically significant differences regarding grade, stage, and FLIPI between the maintenance rituximab and observation groups.

Altogether, 163 FL patients received rituximab chemotherapy at least once in their lifetime during the course of their disease as first-line treatment or in a relapse setting, and only 30 patients had never been treated with rituximab.

Disease Outcomes

OS of All Patients (n = 278) and OS of Patients Treated With Systemic Therapy (n = 193). With a median follow-up of 5.7 years (range, 2-11 years), the estimated 5- and 10-year OS rates for the